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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/733,387	12/07/2000	Gregory Donoho	LEX-0104-USA	7426

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EXAMINER	
LI, RUIXIANG	
ART UNIT	**PAPER NUMBER**
1646	13

DATE MAILED: 01/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/733,387	DONOHO ET AL.	
	Examiner	Art Unit	
	Ruixiang Li	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 6-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 6-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

I. Status of Application, Amendments, and/or Claims

The amendment filed in Paper No. 11 on November 1, 2002 has been entered in full. Claims 6-9 have been added. Claims 1-3 and 6-9 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

II. 35 U.S.C. § 101

The rejection of claims 1-3 under 35 U.S.C. 101, as set forth at pages 2-5 of the previous Office Action (Paper No. 9, June 28, 2002), remains.

Claims 1-3 and the newly added claims 6-9 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well-established utility. The basis for this rejection is set forth at pages 2-5 of the previous Office Action (Paper No. 9, June 28, 2002).

The applicants' response (Paper No. 11, November 1, 2002; hereinafter "Response") argues that the protein of the present invention belongs to the G-protein coupled receptor (GPCR) family, members of which are well known in the art to be commercially valuable drug targets. Thus, the claimed invention has a well-established utility (page 3, 2nd paragraph). This has been fully considered but is not deemed to be persuasive because commercial success is not an indication of utility and the commercial value does not simply render the claimed invention a specific, substantial,

and credible utility. This is because many products may be commercially successful due to reasons unrelated to the use of the products. For example, a pharmaceutical company may wish to purchase a putative GPCR on the chance that it may turn out to be a drug target in future, even though determining such possibility requires substantial further experimentation. However, such substantial further experiment is not acceptable for patentable utiity. In addition, substantial further experiment may have already been done on some of the GPCRs mentioned in the Response and specific functions may have already been known. This is not the case here.

The Response argue that the amino acid sequence deduced from the claimed nucleotide sequence shares over 90% homology with a sequence present in GenBank which has been annotated as "Homo sapiens similar to G-protein coupled receptor 56" (GenBank, Accesion No. XM_169439) and thus it is sufficient to justify that the protein encoded by the claimed nucleic acid is a GPCR (bottom of page 3). This has been fully considered but is not deemed to be persuasive because the annotation for the published sequence is also based upon sequence homology and there is no sufficient and credible information that indicates the published sequence is a truly functional GPCR.

The Response argue that the amino acid sequence deduced from the claimed nucleotide sequence shares 68% percent identity and 78% similarity overall at the amino acid level with a sequence present in GenBank which has been annotated as "Mus musculus Pb99 gene sequence" (GenBank, Accesion No. AF249738). The protein encoded by the gene sequence has been characterized as a G-protein coupled receptor (Mol. Cell. Biol. 20:4405-4410, 2000). This has been fully considered but is not deemed

to be persuasive because (i) the annotation for the published sequence in Genbank is, again, based upon sequence homology and there is no sufficient and credible information that indicates the published sequence is a truly functional GPCR; (ii) careful evaluation of the publication by Sleckman et al. (Mol. Cell. Biol. 20:4405-4410, 2000) leads to the conclusion that this paper asserts that the cDNA encodes a putative protein that has seven hydrophobic domains similar to those of G-protein coupled receptors (see Abstract). Once again, this prediction was based upon sequence homology without sufficient evidence indicating that the protein is functional GPCR; and (iii) even if the cDNA of Sleckman et al. encodes a functional GPCR, the sequence similarity does not render the sequence of the present invention a patentable utility (see below).

The response argues that the references cited by the Examiner do not support lack of patentable utility and the sequence homology with GPCRs is sufficient to justify the functions of the claimed molecules and thus to provide the claimed invention a patentable utility (page 2 of page 4 to 1st paragraph of page 5). This has been fully considered but is not deemed to be persuasive because 35 USC §101 requires disclosure of a specific, substantial, and credible utility. Such a patentable utility has to be a "real world " context of use which does not require significant further research. The instant disclosure asserts that the deduced amino acid sequence encoded by the claimed nucleic acid shares sequence homology with GPCRs without revealing the specific functions or activities of the claimed molecules. In view of the diversity of structure and functions of the proteins, prediction of function using comparative sequence analysis may lead to the creation and propagation of assignment errors if not performed appropriately (See, Peer Bork and Eugene V. Koonin, Predicting

functions from protein sequences--where are the bottlenecks? Nature Genetics 18:313-318,1998). There are putative seven transmembrane molecules, which do not appear to be coupled to a G protein (Ji et al. G-protein-coupled receptors, *J.B.C*, 273:17299-17302, 1998). A change of two-amino acid residues in a protein results in switching the binding of the protein from one receptor to another (Yan et al, Science, 290:523-527, 2000).

While sequence analysis is important, the information provided or "predicted" based upon sequence homology can only be used as guidance in determining functions or activities of a molecule by experiments. Any functions predicted based upon the sequence homology will have to be confirmed ultimately by bench work. Such confirmation whether the claimed nucleic acid encodes a functional GPCR requires undue experimentation. See *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."

The Response argues that the instant disclosure provides a patentable utility citing various case laws (2nd paragraph of page 5 to page 6). This has been fully considered but is not deemed to be persuasive for the following reasons.

First, the Response cites a device case law. The "device" case law deals with "inopertiveness" under 101 (pertains to perpetual motion machines, for example). The claimed invention in the instant case is drawn to an isolated nucleic acid, not a device and the instant rejection under 35USC101 is not directed to inoperativeness, but to a lack of patentable utility of the claimed nucleic acid. Thus, applicants' argument citing a case law regarding a device is irrelevant to the instant case.

Second, while the FDA approval is not a prerequisite for finding a compound useful within the meaning of the patent laws and the requirement for the utility of the claimed invention is different from the FDA standard for drug approval, 35 USC §101 does require a specific, substantial, and credible utility, or well-established utility for an invention. The disclosure asserts the utility of the claimed invention in diagnosis and treatment of physiological or behavioral disorders. However, the disclosure fails to provide any evidence and information on the biological functions of the claimed molecules, and fails to identify a disorder or condition that can be diagnosed or treated with the claimed molecules. Without such sufficient information, how can one skilled in the art to use the claimed invention? See *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."

Third, 35 USC §101 requires disclosure of a specific, substantial, and credible utility. Such a patentable utility has to be a "real world " context of use which does not require significant further research. The Response confuses this requirement with the "further research and development" needed in pharmaceutical composition and drug development. In other words, a patentable utility has to be clearly identified or immediately apparent in the disclosure which has nothing to do with the "further research and development" needed in drug development. For example, determining dosage and administration routes is further research and development, which is acceptable under 35 USC 101 because it is not significant. On the other hand, determining what diseases are to be treated constitutes significant further research and development, which is not acceptable under 35 USC 101.

The Response argues that DNA chips using the claimed nucleotide sequence provide a utility for the claimed invention (last paragraph of page 6 to 1st paragraph of page 6). This has been fully considered but is not deemed to be persuasive because such utility does not provide a specific and substantial utility for the claimed sequence. Since the disclosure does not reveal any activity/functions of the nucleotide sequence or the protein encoded by the nucleotide sequence, one skilled in the art would not know how to use the claimed sequences.

The Response argues that the claimed polynucleotide sequence has a specific utility in mapping the protein encoding regions of the corresponding human chromosome (last paragraph of page 7 to 1st paragraph of page 7). This has been fully considered but is not deemed to be persuasive because such a utility is considered a research utility only designed to identify a particular function of the claimed molecules and is not a substantial utility. See, e.g., *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966) wherein a research utility was not considered a "substantial utility."

The Response argues that persons of skilled in the art, as well as thousand of venture capitalists and investors, readily recognize the utility, both scientific and commercial, of human genomic data (2nd paragraph to 3rd paragraph of page 8) and that the usefulness of the claimed nucleic acid molecules is substantial and credible and well-established. This has been fully considered but is not deemed to be persuasive because the disclosure has failed to provide any information or evidence on the biological functions or activities of the protein encoded by the claimed nucleic acid. Without knowing biological functions of the claimed molecules, one of skilled in the art would not know what to do with the claimed invention. Certainly, human genomic data

have both scientific and commercial value. However, the commercial value does not simply render the claimed invention a specific, substantial, and credible utility, and the general utility of human genomic information does not simply render the claimed nucleic acid sequences a well-established utility.

The Response argues that the requirement set forth in the Action for compliance with 35 U.S.C. § 101 do not comply with the requirement set forth by the Patent and Trademark Office itself for compliance with 35 U.S.C. § 101. The PTO issued numerous patents on plynucleotide sequences that have not been directly shown to be associated "with any disease or condition" (top of page 9). This has been fully considered but is not deemed to be persuasive because each application is examined on its own merit. It should be noted that the examiner has no authority to comment on the validity of the issued U.S. patents.

In summary, the disclosure fails to provide a specific, substantial, and credible utility, or a well-established utility.

III. Claim Rejections Under 35 U. S. C. § 112, 1st Paragraph (Enablement)

The rejection of claims 1-3 under 35 U. S. C. § 112, 1st paragraph, as set forth at pages 5-7 of the previous Office Action (Paper No. 9, June 28, 2002), remains.

The newly submitted claims 6-9 are also rejected under 35 U. S. C. § 112, 1st paragraph. The basis for this rejection is set forth at pages 5-7 of the previous Office Action (Paper No. 9, July 30, 2002).

The applicants' arguments about the patentable utility of the claimed invention has been fully considered but is not deemed to be persuasive for reason set forth above.

The scope enablement rejection related to claim 1, which recites an isolated nucleic acid molecules comprising at least 22 contiguous bases of nucleotide sequence from SEQ ID NO: 43, also remains. The Examiner notes that this scope enablement rejection was written if there were a patentable utility for the claimed invention. The Examiner further clarify that SEQ ID NO:43 is not enabled (due to lack of a patentable utility).

The Response argues that the scope enablement rejection related to claim 1 is improper because (i) the Examiner's comments were not relevant to the established legal standard of enablement; (ii) the Examiner's failure to attribute adequate weight and attention to the detailed level of teaching clearly provided in the specification; and (iii) the reasoning for the enablement rejection provided by the Examiner failed to adequately consider the high level of technical knowledge that can be attributed to those skilled in the art in the filed of the present invention (middle of page 10 of applicants' response), citing various case laws (pages 10-14).

The applicants' arguments has been fully considered but is not deemed to be persuasive for the following reasons, as well as for the reasons set for at pages 5-7 of the previous Office Action (Paper No. 9, September 4, 2002).

The scope enablement issue is judged against the well-established Wands factors, as recited in the previous office action. The key issue here is the breadth of the claim. Claim 1 is drawn to an isolated nucleic acid molecule comprising at least 22 contiguous bases of nucleotide sequence from SEQ ID NO:43. Thus, the claim recites a genus of nucleic acid molecules of any size comprising at least 22 contiguous nucleotides of SEQ ID NO: 43. While some of species of the genus may retain a readily

apparent use if such a use were present for the full-length molecule, the instant disclosure would not be found to be enabling for the whole genus because (i) there is no evidence that 22 residues are sufficient to retain the functions of the full length and (ii) even if so, there is no guidance regarding which 22 residues are sufficient.

If the applicants intend to claim a genus of nucleic acid molecules which encode peptides, the instant disclosure fails to show (i) which portions of SEQ ID NO: 43 are critical to the activity of the protein of SEQ ID NO: 44; and (ii) what modifications (e.g., substitutions, deletions or additions) one can make to SEQ ID NO: 43 will result in protein mutants with the same functions as the protein of SEQ ID NO: 44. The state of the art (See, e.g., Ngo, et al, *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz, et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495) is such that the relationship between sequence of a protein and its activity is not well understood and is not predictable. Excising out portions of a protein or modifications to a protein, e.g., by substitutions or deletions, would often result in deleterious effects to the overall activity and effectiveness of the protein.

On the other hand, if applicants intend to claim for a genus of nucleic acid molecules as being used for primers or probes, the instant disclosure fails to provide information or sufficient guidance on how to make and use the claimed genus. One skilled in the art may be able to use, for example, a nucleic acid molecule consisting of 22 contiguous nucleotide of SEQ ID NO:43. However, one skilled in the art would not be able to use the claimed broad genus to specifically determine, for example, the expression of the instantly claimed nucleic acid in a tissue, due to the unpredictable nature of nucleic acid hybridisation and the possibility that a claimed nucleic acid

molecule may hybridize to a nucleic acid other than the portion of SEQ ID NO: 43. The state of the art is such that determining the specificity of hybridization is empirical by nature and the effect of mismatches is unpredictable, as taught by Wallace et al. (Methods Enzymol. 152:432-443, 1987) and Sambrook et al. (Molecular Cloning, A Laboratory Manual, 2nd Edition, 1989, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, page 11.47).

IV. Claim Rejection Under 35 U. S. C. § 112, 1st Paragraph (Written Description)

The rejection of claim 1 under 35 U.S.C. 112, 1st paragraph (Written Description) as set forth at pages 7-8 of the previous Office Action (Paper No. 9, June 28, 2002) remains.

Applicants argue, citing a number of case laws (pages 14-16), that provision of the nucleotide sequence renders the application in compliance with 35 U.S.C. §112, first paragraph (2nd paragraph of page 15 of the Response) and that the skilled artisan would readily be able to distinguish the claimed nucleic acids (last paragraph of page 15 to top of page 16 of the Response). This has been fully considered but is not deemed to be persuasive for the following reasons. The claim is drawn to a genus of nucleic acid molecules comprising at least 22 contiguous nucleotides of SEQ ID NO: 43. Thus, it encompasses virtually any random sequence of any length as long as it has a stretch of at least 22 consecutive nucleotides of EQ ID NO: 43. The claim does not require that the nucleic acid molecules possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics

of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is comprising at least 22 contiguous nucleotides of SEQ ID NO: 43. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Therefore, only an isolated nucleic acid molecule comprising SEQ ID NO:43, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

V. Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (703) 306-0282. The examiner can normally be reached on Monday-Friday, 8:30 am-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [yvonne.eyler@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

Ruixiang Li
Examiner
January 15, 2003